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Brachytherapy for Residual Intra-Renal Wilms' Tumor

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Key words: brachytherapy; relapsed Wilms' tumor; bilateral Wilms' tumor

C. Pace Duckett (Student, University of Pennsylvania)

We would like to present long-term follow-up data concerning two patients with both kidneys affected by Wilms' tumor whose clinical problems were solved in a unique manner.

The first child, V.A., is now 14 years old. When 13 months of age, in another country, she was found to have a right-sided Wilms' tumor. She was given preoperative dactinomycin (AMD) and vincristine (VCR) and then underwent a right nephrectomy. These drugs were continued in the postoperative period, and she fared well until she was 4½ years old when she was found to have a metachronous Wilms' tumor on the left side.

Doxorubicin (ADR) produced good shrinkage, and she had excision of the lesion which was in the anteromedial aspect of the kidney just beneath the renal pelvis. The margins of excision were not clean so post-operative radiation therapy (to 1,440 cGy in 8 treatment days) was administered to the region of the tumor bed only. Three-drug maintenance chemotherapy with AMD + VCR + ADR was continued, but 2 years later there was a recurrence in the same site on the left. Combination chemotherapy with etoposide and ifosfamide was initiated, the tumor disappeared, and all remained quiescent for 2½ years when there was another relapse in precisely the same spot. This possibility had been foreseen by Dr. John Duckett, Director of Urology, and a contingency plan was in place. This was based on his novel suggestion that brachytherapy methods might solve the problem. First, preoperative treatment with etoposide and carboplatinum shrank the 4 cm mass by 50%. Then the lesion was re-excised, but this time a Foley triple-lumen catheter was introduced and the balloon positioned in the cavity. Details regarding the after-loaded brachytherapy employed will be provided by Dr. Goldwein later.

The second patient is E.K. who also was referred here after primary management elsewhere. He was found to have a left-sided Wilms' tumor when 2 years old, and underwent a left nephrectomy with postoperative AMD plus VCR. Nephroblastomatosis was identified in the specimen. A doubtful lesion on the right side was followed for about 3 years, when this centrally located lesion started to grow. Preoperative ADR was given at that time with partial response of the tumor, which then was excised and a balloon catheter placed in the defect. Again, the details regarding radiation therapy will be presented by Dr. Goldwein. Let me anticipate by saying that three drug chemotherapy (AMD + VCR + ADR) was continued postoperatively.

Now, Drs. Duckett and Zderic, will you please describe the operations you performed in these two children?

John W. Duckett, MD (Pediatric Urologist)

The left renal tumor in V.A. was confined to the peripelvic area on the lower pole. It was stuck significantly to the pelvis but the four silver clips left after resection of the previous tumor were easily dissected free without any evidence of tumor invading the pelvis. The lesion itself was excised en bloc with a rim of normal parenchyma around it and we felt that we had gotten a good margin. We sent several biopsies from the tumor bed right against the pelvis to see if there was any remaining viable tissue.

The lower pole collecting system was closed and the bivalved kidney was brought back together over an 18 French Foley catheter, the balloon of which lay perfectly in the spot where the tumor was resected. To do this, we

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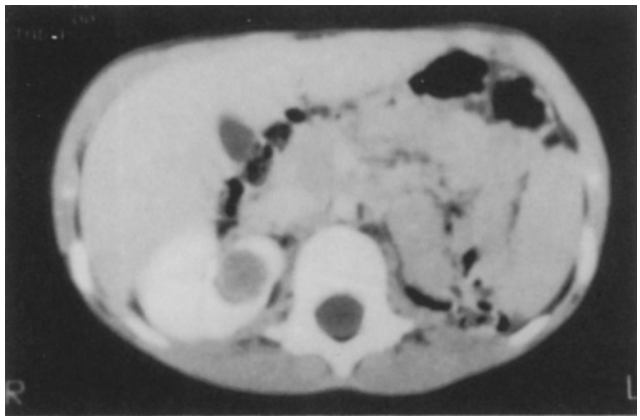

Fig. 1. CT scan. The tumor is clearly seen as a non-opacified defect within the substance of the sole remaining (right) kidney.

modified the 18F Foley catheter by cutting off the distal tip and tying a silk suture to maintain the balloon capacity. This permitted placement of the partially inflated balloon (2–3 ml) in the tumor fossa. The internal lumen of the catheter within the balloon diameter was carefully measured so that a radioactive source could be inserted precisely in the middle of the cavity to deliver radiation to the required depth. A dummy after-loading tube was inserted within the second lumen through a side-wall slit carefully avoiding the balloon inflating lumen. The catheter was fixed to the skin with a suture so that the course from the kidney was straight.

Her kidney was clamped for 20 minutes with one "breathing spell" at 10 minutes. Prior to clamping, mannitol was infused and cold slush was used to cool the kidney during the ischemic phase. She immediately began to make urine after reperfusing and has done so ever since. Her creatinine the following morning was 1.3 mg per dl. She had a mild blood pressure elevation the first night.

Dr. Zderic, your procedure was rather similar, was it not?

Stephen Zderic, MD (Pediatric Urologist)

Yes, in many ways. E.K.'s lesion was located in the upper posteromedial portion of the cortex (Fig. 1), and was successfully sampled by needle biopsy, the findings of which were consistent with Wilms' tumor. An angiogram revealed a single renal artery and classical intrarenal anatomy. The child was prepared for a traditional exploration in which we would have full access to the peritoneum, but we positioned him in a modified right flank position so as to provide maximal renal exposure. With the kidney fully exposed, no obvious cortical mass was noted, but by use of the CT scan and ultrasound it was apparent where our nephrotomy needed to be placed.

First, it was necessary to take steps to preserve renal parenchymal function. Ten grams of i.v. mannitol were administered, followed by the application of a rubber dam and a slush of Ringer's lactate. This regional hypothermia produces intrarenal temperatures of 18–24°C, and allows for clamping of the renal vessels for up to 1 hour with minimal cellular damage. In contrast, warm ischemia is tolerated for only 10 to 15 minutes. Experimental evidence suggests that much of the damage from ischemia is secondary to free radicals and a breakdown of cellular ionic gradients. Ischemic cells lose their ability to maintain their cytosolic calcium within normal ranges, and at some point the process becomes irreversible leading to cell death. Hypothermia alone is protective by slowing down the metabolic rates of the key enzymes involved in maintaining these critical ionic gradients. The use of mannitol induces a brisk diuresis once the vessels are unclamped, but it also serves as a free radical scavenger (to be fully effective it must be given in advance). Allopurinol serves to trap free radicals; and it, too, was given to this patient preoperatively. There are experimental data indicating that one might also use calcium channel blockers to protect parenchymal function, though we opted not to use them in this setting.

With the kidney protected by the addition of mannitol and the application of regional hypothermia, the renal artery and vein were clamped. A small 4 cm nephrotomy was made in the region above the tumor (Fig. 1), and the mass lesion was very easily shelled out (Fig. 2). A rim of tissue remained free of gross tumor, though some cellular dysplasia was noted. Biopsies were taken from this area. At this point, the Foley catheter was placed within the cavity and the balloon was inflated with the predetermined volume of air so that exact dosimetry for brachytherapy could be calculated. The renal capsule was then closed over the catheter with the use of chromic stitches and Surgicel® (Johnson & Johnson Medical Inc., Arlington, Texas 76004-3130) pledgets (Fig. 3). The renal vessels were unclamped and normal renal color returned signifying good perfusion. The Foley catheter produced ample urine within 15 minutes, and hemostasis was excellent. At the completion of wound closure, the total blood loss was 80 cc.

Joel Goldwein, MD (Pediatric Radiation Oncologist)

In both instances, prepared isodoses for the sources (18.6 and 21.0 mCi, respectively) were available. Our objective was to deliver doses between 16 and 20 Gy to the tumor bed over a period of about 24 hours. Thus, the dose rate in both cases was 80 cGy/hour maximum. The dose fall off was abrupt; $\frac{1}{2}$ and $1\frac{1}{2}$ cm from the surface of the balloon, the dose rates were 15 and 6 cGy/hour, respectively.

Once the patients were sufficiently recovered from surgery, they were placed in adequately shielded rooms. The balloons were re-inflated to the predetermined amount, the dummy sources were removed from the cath-

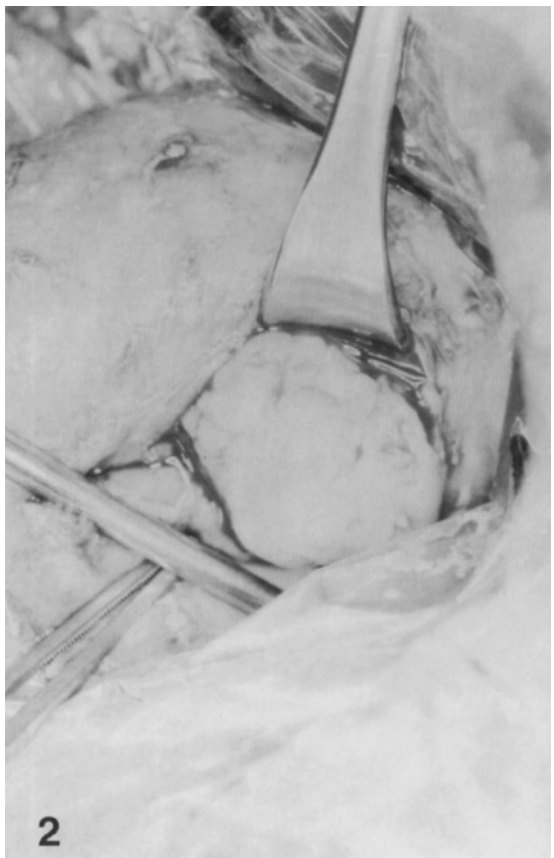

Fig. 2. The whitish tumor within a bloodless field lies between the retractor superiorly and the clamps inferiorly.

Fig. 3. Appearance of the kidney after tumor removal and closure. The catheter (arrows) exits the kidney substance to the left inferiorly. Surgicel® pledgets, visible as curvilinear, dark granular objects, overlie the renal capsule.

eter and active sources were placed for the duration of the implant. After the time was up, the sources were easily removed, the balloons were deflated and the catheters were simply pulled out. There was minimal discomfort associated with this maneuver—or during the entire brachytherapy period, for that matter.

C. Pace Duckett. Both patients are free of disease and off therapy, V.A. for 4½ years and E.K. for 3 years.

Starting 1 year or so after brachytherapy, V.A. developed evidence of renal dysfunction associated with loss of function of the lower pole of the remaining left kidney, for reasons that are not entirely clear. The operative notes describe the proximity of the tumor to the branches of the renal artery supplying the inferior portion of the kidney. It is possible that the vessel wall was damaged during the dissection. It certainly would have been at the high isodose line of the subsequent brachytherapy plane, remembering this region had already received external beam radiation to 1,440 cGy. Probably the combination of radiation and surgical manipulation contributed to this result. In any event, she seems fit and is growing normally according to follow-up information received from her physicians abroad.

The second patient, E.K., also is being followed out of the country, but appears to be entirely well without any evidence of recurrent disease or renal dysfunction.

Synchronous bilateral disease occurs in about 5% of all patients with Wilms' tumors [1,2]. The children generally are younger in age than those with unilateral disease (mean ages: 2.5 and 3.5 years, respectively) [1,3]. The outlook for those with bilateral Wilms' tumors is good, their survival rate in two large series ranging from 70 to 87% [1,2]. Metachronous lesions occur in about 1% of patients with Wilms' tumor, and their outlook is generally thought to be worse. For example, Jones et al. reported a 39% survival rate for 18 patients; it was 56% in the 25 patients studied by Coppes et al. under those circumstances [2,4]. A more recent review by Shearer et al. of their institutional experience found an equal outlook for their seven children with metachronous disease as compared with 29 patients with synchronous lesions: 71 and 70%, respectively [5]. A possible explanation for the less satisfactory result in children with metachronous lesions is the fact the tumor has regrown despite first-line chemo-

therapy, which usually consists of AMD + VCR ± ADR. That is what happened in the two patients being reported here: attempts at retrieval with partial excisions and radiation therapy in the case of V.A. and change of chemotherapy in the case of E.K. did not prevent a recurrence of disease. Furthermore, the lesions were critically placed in such a way that a partial nephrectomy could not be performed. A recent review of renal failure in 39 patients with bilateral Wilms' tumor conducted by Ritchey et al. found that bilateral nephrectomy was the single most common cause of that problem, being responsible for 24 of the cases [6]. Rendering patients anephric is clearly something to be avoided if at all possible. Survival under those circumstances is poor. There are difficulties in managing patients with dialysis until their prognosis is sufficiently clear that a renal transplant can be advised. Two years has been recommended for this period of observation. Dr. John Duckett's idea was therefore very attractive when he suggested after the first relapse in patient V.A. that the balloon technique here described be employed should she relapse in the same location a second time. This brachytherapy maneuver appears to have been successful in controlling residual disease in both children so that bilateral nephrectomies could be avoided.

Alfer et al. also avoided bilateral nephrectomies in the patients they reported who underwent tumor excision from the depths of the kidney [7]. The surgical technique they described is very much the same as that outlined by Drs. Duckett and Zderic. Their patients, however, were managed in that way per primum, and continuation chemotherapy sufficed to obliterate the residual tumor at the margins of resection. This also has been the experience in the National Wilms' Tumor Study [1,6]. Our two patients had, however, demonstrated their tumors to be chemoresistant, the tumor having recurred despite aggressive chemotherapy using multiple agents and radiation therapy in the first case. The challenge was to excise the tumor from each remaining kidney while preserving the maximum amount of renal parenchyma. An integrated multi-disciplinary team consisting of pediatric oncologists, urologists, surgeons, and radiation oncologists was mobilized to approach the problem in the unique way described. Use of this technique preserved kidney function because the dose to the remaining renal parenchyma was low, estimated to be about 10% of the tumor dose 2 cm from the source in both patients or not more than 200 cGy in either child.

Brachytherapy has, of course, been used extensively for cancer arising in natural body cavities for decades, but these are the first reported instances where the technique was used to control residual Wilms' tumor in a solitary kidney [8].

In summary, our purpose in presenting these two patients is not to review either the management of bilateral Wilms' tumors, or the broad field of brachytherapy. Rather, it is to demonstrate how this radiotherapeutic technique was successfully adapted to a particular problem in patient management. We hope, in so doing, to encourage further use of brachytherapy methods in pediatric oncology.

ADDENDUM

A third patient has been managed in this way at another institution, and is the subject of a separate report which provides greater radiotherapy details concerning all three of these children.[1] At last word, that child also is faring well 13 months after the procedure.

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SERIES EDITOR'S NOTE

Imaging studies were important in accurately defining the location and boundaries of the lesions discussed in this Proceedings. Radiology has progressed beyond simple planar radiography (x-ray filming), epoch-making though that technique was and remains.

[1]Thoms WW Jr et al: A technique for the use of afterloading cesium brachytherapy in renal sparing irradiation of bilateral Wilms tumor. Int J Rad Oncol (in press).

When W. Roentgen discovered the x-rays in 1895, he appreciated that there was radiant energy coming from the Crooke's tube he was energizing. He did not know the nature of these rays and, borrowing a term from *algebra* for an unknown, he named them *x-rays*. It is interesting that he objected to the application of his name to these rays believing that the term "roentgen rays" demeaned his family name. *Ray* comes from the Latin *radius* (spoke of a wheel). *Radiation* was derived from the notion that beams of light seem to radiate from the source, and reminded the viewers of *radii*.

Algebra is from the Arabic *al-jabr* meaning bone setting or reduction of fractures. From this came the notion of the reduction of a numerical term to its elements through algebraic manipulations. There are other words in everyday use in science derived from Arabic. *Algorithm* is named after an Arabian mathematician, al-Khuwarizmi, the Arabic being in translation, "the native of Khuwarizm" (*Khiva**). *Alkali* is from *al-qali;* literally, "saltwort ashes." Saltwort is a plant growing in salt marshes and alkaline regions, and its ashes added to water produce an alkaline supernatant. *Alchemy* is from the Greek *khemioa,* transliterated as *al-kimia* in Arabic, always with the same meaning. *Alcohol* presents interlingual complexities. It comes from *al-kuhul* from *khol,* a cosmetic used to blacken the eyelids or eyebrows. *Khol* from the Hebrew *kakhal* (to stain or paint) is also known as *coryllium*—Latin from the Greek *kollyrion* = eye poultice (from Greek *poltos* via Latin *pultem* = thick *pap* (of Scandinavian origin). *Khol* originally was finely powdered antimony (itself perhaps derived from the Arabic *ithmid*), but became applied to anything obtained by sublimation (directly from the Latin with the basic meaning of "refined"); hence, the quintessence (Latin: fifth essence = the purest form) of a substance. First applied to solids, the term became extended to liquids starting with the quintessence of wine (Latin: *vinum* from the Greek *oinos*) and eventually to its chemical meaning.

By now it is obvious that many words starting with *al-*, not only those in science, can be traced back to Arabic; e.g., *almanac* (*al-manakh*). It is therefore redundant to say, "the almanac", "the" being inherent in the word itself. Not all scientific words from the Arabic start with *al-*, however; e.g., *azimuth* from *as-sumut* = the way.

The extraordinary contributions to mathematics, medicine, and science stemming from the several civilizations of Greece and the near East still resonate in words we use every day.

*Khiva was a khanate south of the Aral Sea in an area now encompassed by the (ex-Soviet Socialist) Republics of Uzbekistan and Turkmenistan.